REMARKS

Reconsideration and withdrawal of the rejections of the application are respectfully requested in view of the amendments and remarks herewith, which place the application into condition for allowance. The Examiner is thanked for courtesies extended in the course of the interview on August 6, 2002.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 42-48 are pending in this application. Claims 27-29 and 33-39 have been cancelled; claims 42-48 have been added. No new matter is added by this amendment.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. §112. The amendments of and additions to the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Support is found throughout the specification and from the pending claims. Furthermore, it is explicitly stated that the herewith amendments should not give rise to any estoppel, as the herewith amendments are not narrowing amendments.

Refund of Extension Fee

Attached hereto is a copy of the postcard and certificate of first class mailing, demonstrating that a response to the October 23, 2001 Office Action was mailed before the due date of November 23, 2001. Please refund the fee charged to Deposit Account No. 50-0320 for a one month extension to the deposit account.

Data Submitted Previously Now Presented in Declaration Form

The amendment filed on December 4, 2001 included six studies carried out by the Applicants or assignee. The results of these studies are relevant to the invention as claimed and were submitted for consideration during the August 6, 2002 interview in the Declarations of Drs. Jonathan Lamb and Margaret Dallman. To clarify the relevance of the studies:

> Study 1 (Lamb) shows *inter alia* that Notch ligand therapy may be used to reduce an immune response to a chosen antigen *in vivo*, and provides a further model of treatment of allergy;
>
> Study 2 (Lamb) shows *inter alia* that the reduction in immune response may be directed to a chosen antigen;

Study 3 (Lamb) shows *inter alia* that Notch ligand therapy may be used to reduce an **established** immune response to an antigen *in vivo*, and provides a further model of treatment of allergy;

Study 4 (Lamb) and Study 2 (Dallman) show *inter alia* that Notch ligand therapy has a lasting effect;

Study 5 (Lamb) shows *inter alia* that the reduction in immune response resulting from Notch ligand therapy can be transferred by T cells; and

Studies 1 and 2 (Dallman) show *inter alia* that graft rejection of cells and/or organs may be effectively treated with Notch ligand therapy.

Most of this data was also presented at the August 6, 2002 interview in the form of a PowerPoint presentation, summarized in the Declaration of Dr. Brian Champion. Original copies of the Declarations of Drs. Lamb, Dallman and Champion are attached.

Priority Claim

The Interview Summary, mailed on March 12, 2002, acknowledges Applicants' claim for priority under 35 U.S.C. §119 to U.K. application Nos. 9719350.2, 9715674.9, 9623236.8 and GB97/03058, filed in Great Britain on November 7, 1996, July 24, 1997, September 11, 1997, and November 6, 1997 respectively.

Objection to the Disclosure

The typographical errors on pages 10 and 12 that were pointed out in the Office Action have been corrected by amendment.

II. THE REJECTIONS UNDER 35 U.S.C. §112, 1ST PARAGRAPH, ARE OVERCOME

The Specification Contains Adequate Written Description

Claims 27-29, 33-37 and 39 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking written description.

The Office Action alleges that one of ordinary skill in the art could not visualize a Notch ligand, with the exception of full length Delta or full length Serrate, which could be administered in a method of treating T-cell mediated disease or infection without a description of the structural basis for the biological interaction of T cells with Notch ligands. The Office action further alleges that there is no "description of the structural basis for the biological interaction of T cells with notch ligands". The rejection is traversed.

Fragments/derivatives of Notch ligands can readily be generated by following the guidance at page 2 of the specification that: "The Notch ligands have a diagnostic DSL domain (D.Delta, S, Serrate, L, Lag2) comprising 20-22 amino acids at the amino terminus of the protein..." Claims 42 and 43 reflect that the Notch ligand comprises a DSL domain.

Furthermore, Example 2 (page 16) of the specification discloses a fragment/derivative of Delta comprising the extracellular domain, viz: "a fusion protein that contains the extracellular portion of Delta 1 linked to the human IgG1-F_c domain" (emphasis added).

Moreover, Notch and Notch ligands, as found in mammalian immune cells, are understood to have substantially the same structure as Notch and Notch ligands found in other eukaryotic cells. Thus structural information reported for Notch and Notch ligands in other cells is entirely relevant to immune cells generally and T cells specifically.

There was already extensive discussion of Notch ligand structure in the published literature when the present application was filed. For example the Artavanis-Tsakonas et al article states at page 228 that:

> "The DSL region appears to be important for Notch function .... In contrast the intracellular domains of all the putative Notch ligands display no significant sequence similarity, and replacement of most of the Lag-2 intracellular domain with a β-galactosidase fusion protein has no discernable effect on Lag-2 function" and further that: " the observation .... suggests that there is a high degree of functional conservation in the ligand-binding properties of Notch proteins from different species."

This article, the references submitted to the Examiner at the August 6, 2002 interview, (Henrique et al., 1995; Lindsell et al., 1995; Nye and Kopan, 1995) and the references cited in the application (which are incorporated into the specification by reference) clearly demonstrate the structural similarity between a wide variety of Notch ligands in different organisms. Attention is drawn, for example, to Figure 1 of Henrique et al., 1995, at page 778; to Figure 1 of Lindsell et al.. 1995, at page 910; and to Figure 1 of Nye and Kopan, 1995, at page 967. Attached is a table showing that many Notch ligands were known in various organisms at the time this application was filed

It should also be clearly understood that the present invention does not reside in identifying Notch ligands *per se*, or even their sequences/structures, but rather in identifying a

new and inventive method of use for them. In particular, the detailed nucleotide and amino acid sequences of a large number of representative Notch ligands were well known in the art. See, for example the PCT publications cited in the present description at page 10, lines 15-17.

The key DSL domain structure described *inter alia* at page 2 of the present description (see passage quoted above) were also well known from these and other documents, including Artavanis-Tsakonas et al. (see, for example, Figure 2 thereof and the passage at page 228 headed "Ligands for Notch").

Thus the term "DSL" is clearly recognized and understood as a term of art in this field, such that no further description of it is necessary. The present description as filed clearly therefore provides "a recitation of structural features common to the genus" in accordance with the cited decision in *Regents of the University of Califomia v. Eli Lilly & Co.*

In this connection, it is stated in the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, as cited by the Examiner (II. 3 (a) at page 1106) that "[t]he description need only describe in detail that which is new or not conventional." (*Hybritech v Monoclonal Antibodies*, 802 F.2d at 1384, 231 USPQ at 94). Thus it is not necessary for the instant description to provide further details of Notch ligand sequences, structures etc which were already well known and understood in the relevant art at the time of filing.

The Specification is Enabling

Claims 27-29 and 33-39 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. The Office Action alleges that although the examples "demonstrate a suppressive effect of full length serrate and full length Delta on T cell priming of naive cells and stimulation of primed T cells in response to specific antigens, it is not clear from the instant disclosure how these results enable one of skill to practice a method of treating any T-cell mediated disease or infection as recited in the instant claims, since **no T cell mediated diseases or infections were disclosed to be treated**." (emphasis added)

To the contrary, Examples 5 and 6 of the present description provide *in vivo* models for the treatment of allergy, and further such models are provided in Studies 1 to 5 in the Declaration of Dr. Lamb. In addition, Study 2 of the Declaration of Dr. Dallman directly shows treatment of graft rejection by administration of Notch ligand. Further, the Declaration of Dr. Brian Champion demonstrates that Notch ligands can be used to control activity of T cells with a wide

range of different antigen specificities. The principle of the invention is of a general application and the mechanism involved relates to the underlying T cell activity, which is not restricted to any particular disease or indication.

The Office Action cites the Jaleco et al. and Janeway references as indicative of unpredictability in the art; however, these references are irrelevant as they relate to hemopoiesis and cell differentiation in the central immune system (such as thymus and bone marrow), rather than immune responses in the peripheral immune system.

Thus, even if Notch signalling in hemopoiesis and cell differentiation in the central immune system is "unpredictable" (arguendo) this is an entirely different biological system which is not relevant to the immune responses in the peripheral immune system of the present invention. To the contrary, the work conducted in the peripheral immune system (as presented in the instant description and Declarations) is notable for its consistency rather than any unpredictability, in that the same general reduction in immune response was seen in both mouse and human cells, and with a wide variety of different peripheral T cells (for example Lymph Node Cells (LNCs) in Example 4 of the specification, spleen cells in Study 1 of the Declaration of Dr. Champion and T cell clones in Example 7 of the specification) and with a wide variety of different antigens (for example a Der p I epitope in Examples 4, 5, 6 and 10 of the specification; hemagglutinin (HA) in Examples 7, 8 and 9 of the specification, Ovalbumin in Example 4 of the specification, and a wide range of tissue antigens in Studies 1 and 2 of the Declaration of Dr. Dallman).

The Office Action alleges that there is insufficient guidance in the specification to allow the skilled artisan to predict 1) which Notch ligands interact with Notch and effect T cells and 2) which fragment or derivative of a Notch ligand could be administered to treat T-cell mediated disease or infection.

To the contrary, as noted above, such guidance is provided at page 2 of the instant specification and also in the art known at the time of filing of the present application (see for example Artavanis-Tsakonas et al as discussed above). It would have been well within the routine skill of the art to follow such guidance. Moreover, the skilled worker could readily determine whether or not any individual Notch ligand was active by performing any one or more of a wide range of routine assays which were well known in the art at the time the present

application was filed. Such assays are described, for example, at page 35 (section 5.7) of WO 96/27610 (acknowledged at page 10, lines 26 of the present description).

Contrary to the suggestion in the Office Action, the data provided **do** show the effect of Notch ligand therapy on "the activity of all the cells that make up the sum total of the immune response". It should be noted that the *in vivo* Examples presented in the specification and Declarations of Drs. Lamb, Dallman and Champion (e.g. Examples 5, 6 and 10 of the specification and Studies 1 to 5 of the Declaration of Dr. Lamb, Studies 1 and 2 of the Declaration of Dr. Dallman and Study 2 of the Declaration of Dr. Champion) relate to systemic effects in **a complete animal immune system** and thus **necessarily** relate to the "sum total of the immune response" as emphasised by the Examiner.

Therefore, it is respectfully submitted that undue experimentation would not be required to practice the invention. And, reconsideration and withdrawal of the Section 112, first paragraph, rejections are solicited.

III. THE REJECTIONS UNDER 35 U.S.C. §112, 2ND PARAGRAPH, ARE OVERCOME

Claim 28 was rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Claim 28 has been cancelled by this amendment, obviating the rejection.

CONCLUSION

In view of the remarks and amendments herewith, the application is in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited.

Respectfully submitted,

FROMMER LAWRENCE & HAUG LLP
Attorneys for Applicants

By: 

Thomas J. Kowalski
Reg. No.: 32,147
Telephone: (212) 588-0800

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

On page 10, line 21:

The *Notch*-ligands of use in the present invention are preferably *Delta* or *Serrate* family member proteins or polypeptides or derivatives thereof. These are preferably obtained using standard techniques of recombinant technology well known to the person skilled in the art. Appropriate gene sequences for use to generate such compounds of the present invention may be obtained from publications such as WO 97/01571, WO 96/27610 and WO 92/19734. The invention is not however in any way limited by the *Notch, Delta* and *Serrate* [invention is not however in any way limited by the *Notch, Delta* and *Serrate*] sequences disclosed in these publications. More preferably, such *Notch, Delta* or *Serrate* or family members, proteins or polypeptides or derivatives therefrom are fragments of the extracellular domains of *Notch, Delta* or *Serrate*, or family members or are derivatives of such fragments. As used herein, the term "*Notch* ligand" further includes any ligand or ligand family member that interacts with a *Notch* protein family member and includes the group of proteins referred to as "toporythmic proteins" i.e. the protein product of the *Delta*[,] and *Serrate*[, *Deltex* and *Enhancer of split*] genes as well as other members of this gene family identifiable by virtue of the ability of their gene sequences to hybridize to, or their homology with Notch, Delta or Serrate proteins, or the ability of their genes to display phenotypic interactions.

On page 12, line 11:

The term "derivative" as used herein, in relation to proteins or polypeptides of the present invention includes any substitution of, variation of, modification of, replacement of, deletion of or addition of one (or more) amino acid residues from or to the sequence, providing that the resultant protein or[on] polypeptide possesses the capability of modulating *Notch-Notch* ligand interactions.

On page 12, line 18:

The term "variant" as used herein, in relation to proteins or polypeptides of the present invention includes any substitution of, variation of, modification of, replacement of, deletion of or addition of one (or more) amino acid residues from or to the sequence, providing that the resultant protein or[on] polypeptide possesses the capability of modulating *Notch-Notch* ligand interactions.